REMARKS

In the Official Action dated July 10, 2003, claims 1-20, 29, and 33 have been rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Chahwala *et al.*, U.S. Patent No. 6,080,761 (hereinafter "Chahwala '761") in view of Foster, U.S. Patent No. 6,333,342 (hereinafter "Foster '342") and further in view of Budavari *et al.*, *The Merck Index*, 12th edition (hereinafter "The Merck Index").

This response addresses each of the Examiner's rejections. Accordingly, the present application is in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The Examiner has based his rejection upon a disclosure in The Merck Index and upon what applicants believe to be an unfounded assumption about the prior art. Applicants respectfully dispute both premises of the Examiner's reasoning. In disproving these bases, Applicants will show clearly that the Examiner has fallen short of establishing a *prima facie* case of obviousness.

The Examiner has cited The Merck Index as disclosing the racemic mixture of amlodipine isomers and has alleged that applicants are "merely claiming the racemate of amlodipine." Unfortunately, applicants must respectfully point out that the Examiner has mischaracterized the present invention. No claim of this invention recites a racemate.

Applicants respectfully question the Examiner's use of the word "racemate." As is well-known in the art, this technical term denotes a mixture containing exactly *equal* amounts of a pair of enantiomers. Such a mixture is usually the result of a synthetic procedure that lacks control of the stereochemical course of a reaction. By contrast, the claimed invention is an intentional mixture of the R(+) and S(-) compounds in, by design, *non-equal* amounts. The composition of this mixture has been optimized with respect to the very different physiological effects (discussed below) of the two compounds.

Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw his rejection based on the teaching of The Merck Index.

In the latest Office Action, the Examiner has also maintained his earlier rejection under 35 U.S.C. §103(a) despite applicants' argument in the March 20, 2003 response that by teaching the individual enantiomers -- R(+) in the case of Chahwala '761 and S(-) in the case of Foster '342 -- these two references teach away from a combination of the two isomers. The Examiner alleges that Applicants have not provided unexpected results which demonstrate the superiority of the claimed ratio of enantiomers. Applicants respectfully respond that the Examiner has not provided the basis for requiring such a showing.

To review the teaching of the cited references, Applicants note initially that the two amlodipine enantiomers have distinct physiological effects: the R(+) isomer promotes the formation of NO and the S(-) isomer is a Ca^{+2} channel blocker. (Applicants observe that The Merck Index, discussed above, discloses racemic amlodipine as the earliest known form of amlodipine and also states that most of the calcium channel blocking activity resides in the S(-) isomer. The Merck Index makes no mention of the activity of the R(+) isomer as a producer of NO and, consequently, as an inhibitor of smooth muscle cell migration.) Chahwala '761 discloses that the R(+) isomer promotes the formation of NO and, in so doing, is an inhibitor of smooth muscle cell migration. Foster '342 discloses that the S(-) isomer is a Ca^{+2} channel blocker and, as such, is an antihypertensive (*i.e.*, causes a drop in blood pressure).

Reviewing the fundamental points of the present specification, Applicants note that the present invention is based on the clinical discovery that the maximum dose of amlodipine racemate that can be administered to a patient in need of treatment for stenosis or atherosclerosis (for which only the NO-generating R(+) isomer is effective) is dictated by the amount of the S(-) isomer that the patient can tolerate before an unacceptable drop in blood pressure. Thus, the antihypertensive effect of the S(-) isomer

imposes an artificial, unnecessarily low limit on the amount of the R(+) isomer that can be administered when the racemate is used. This clinical limit was the deficiency in the prior art which the present invention was designed to overcome.

The present invention overcomes this deficiency in the prior art by providing a mixture comprising an optimal proportion of the enantiomers which maximizes the NO-induced effects of the R(+) isomer while still providing some of the antihypertensive effect of the S(-) isomer. As indicated at page 5 of the specification, the optimized ratio of R(+) to S(-) isomer is in the range 2:1 to 8:1, ideally about 5:1. The present invention provides that such mixtures can be prepared by three distinct methods: by direct combination of suitable amounts of the two enantiomers; by addition of an appropriate amount of the R(+) enantiomer to a racemic mixture; and by preparing mixed crystals containing the required ratio of the two enantiomers. (See specification, at page 6, lines 20 – 28)

Reviewing the reasons for rejection as set forth in the Office Actions dated November 20, 2002, and June 6, 2002, Applicants respectfully submit that the Examiner has not established a factually supported *prima facie* case of obviousness, as case law requires. Accordingly, Applicants have no obligation to produce evidence of non-obviousness.

Establishment of a *prima facie* case of obviousness requires three criteria: i) a suggestion or motivation, either in the prior art references themselves or in the knowledge generally available to the skilled artisan, to modify or combine the references; ii) a reasonable expectation of success; and iii) a teaching or suggestion of all of the claim limitations in the prior art reference or combination of references. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Moreover, under MPEP 2142, an Examiner is required to "step backward in time and into the shoes worn by the hypothetical 'person of ordinary skill in the art' when the invention was unknown and just before it was made. Knowledge of applicants' disclosure must be put aside..."

Applicants respectfully submit that none of the issued Office Actions have either i) documented a suggestion or motivation to combine the references in the prior art or ii) established that the person of ordinary skill in the art would be motivated to combine the references. Applicants respectfully note that the Examiner's sole attempt to provide the required motivation or suggestion to combine references is merely his own *ipse dixit* at page 4 in the June 6, 2002 office action, contained in the following two statements:

> Clearly, one skilled in the art would assume that combining of the two isomers into a single composition possessing the same anti-hypertensive activity will give an additive effect in the absence of evidence to the contrary. (June 6, 2002 Office Action, page 4)

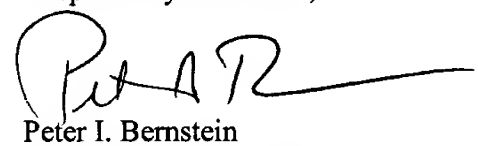
and

> The instant invention differs from the cited references in that the cited references do not teach the applicants' preferred ratios by weight of the R(+) isomer to the S(-) isomer as set forth in claims 1 – 4. However, to determine a ratio of these two isomers, each having optimum therapeutic index, [is] well within the level of one having ordinary skill in the art, and the artisan would have been motivated to determine optimum ratios of each isomer to get the maximum effectiveness. *ibid.*

Applicants respectfully submit that the Examiner's assertions embody an impermissible hindsight which is based upon the applicants' disclosure. Specifically, the conclusion of obviousness in the Examiner's remarks quoted above is based on the mere fact that physically combining the R(+) and S(-) compounds in any proportion was within the capabilities of one of ordinary skill in the art. However, the *effective*, optimal, claimed proportion had to be determined through research and experimentation, in the absence of any expectation that an ideal proportion could be found. Case law has established that, absent an objective reason in the prior art for the claimed combination or modification, even in the case of the technical capability of producing the claimed invention, such a conclusion is improper. *Ex parte Levengood*, 28 USPQ 2d 1300 (Bd. Pat. App. & Inter.1993). See also MPEP 2143.01.

In light of the arguments presented above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a). Applicants respectfully submit that this application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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